REMARKS

Applicants wish to thank the Examiner for the courtesy of a teleconference on August 10, 2004, wherein the Examiner clarified comments set forth in the Office Action mailed on July 27, 2004. In accordance with the Examiner's instructions, applicants are resubmitting herewith an amended version of the entire communication filed on April 7, 2004. Applicants believe that the amendments to the communication, which are directed to setting forth entire paragraphs wherein amendments to the specification are indicated, renders the presently submitted communication fully responsive. No new matter is introduced via these amendments.

Applicants have amended the specification to list appropriate SEQ ID NOs: for sequences presented therein. The indicated sequences are identified by SEQ ID NOs: in the Sequence Listing previously submitted in paper and computer readable form June 27, 2001. No issue of new matter is introduced by these amendments. Accordingly, applicants believe that the specification as presently amended satisfies the requirements set forth under 37 C.F.R. 1.821(d).

Applicants acknowledge that the requirement for restriction has been deemed proper and is, therefore, made final. Accordingly, claims 19-33, 40-41, and claims 36 and 37 (as directed to the non-elected species of Group II) are withdrawn from further consideration as being drawn to non-elected inventions. Claims 34, 35, 38, 39, and 36 and 37 (as directed to the elected species of Group II) are currently under examination. Although the Examiner did not indicate that claims 36 and 37 (as directed to the elected species of Group II) remain under consideration, applicants anticipate that this is correct. Applicants anticipation is based on an understanding that this is proper, based on the nature of requirement for restriction. Clarification is requested in this regard.

Claims 34 and 39 have been amended to more clearly set forth aspects of the invention. Accordingly, claims 34 and 39, as amended, and dependent claims therefrom are under consideration.

Support for the amendments to the claims is found throughout the specification and in the original claims. Specifically, support for amendment to claim 34 is presented in original claims 19-26, 28-31 and 34 and in the specification, for example, at page 2 line 21 through to page 3, line 13, wherein chimeric receptors of the invention and their

characteristics are described; at page 4, lines 5-20, wherein particularly useful ligand association domains are illustrated; at page 4, line 31 through to page 5, line 13, wherein examples of intracellular domain sequences are presented; at page 5, line 32 through to page 6, line 3, wherein suitable transmembrane domains are mentioned; and at page 6, line 28 through to page 7, line 4, wherein spacer domains are described. Support for amendment to claim 39 is presented in original claims 38 and 39 and in the specification, at page 15, lines 2-6 and in Figure 3, wherein pHMF374 is described. No issue of new matter is introduced by these amendments.

The Examiner has objected to the disclosure because it does not include a section entitled Brief Description of the Drawings. Applicants submit herewith a Brief Description of the Drawings section for incorporation into the specification. Support for this passage is presented in the Figures 1-5 as originally submitted. No issue of new matter is introduced by this amendment. Applicants believe that the present amendment to the specification addresses the objection and is, therefore, believed to curative thereof.

The Examiner has indicated that the specification includes reference to the pBluescript ks+ trademark, which must be capitalized or accompanied by the ™ or ® symbol. Applicants have amended the specification at the indicated passages to address this requirement. No issue of new matter is introduced by this amendment.

Claims 34, 35, and 38 have been objected for being dependent on claim 19, which is directed to a non-elected invention. To address the objection to claim 34 and dependent claims therefrom, claim 34 has been amended to include all of the features of the chimeric receptor of claim 19. By this amendment, applicants believe that they have addressed the objection to claims 34, 35, and 38.

Brief Summary of the Invention

The presently claimed invention is directed to DNA encoding chimeric receptors which contain two independent polypeptide chains, each of which contains an extracellular ligand association domain attached to a signaling domain through a transmembrane and a spacer domain. Each polypeptide is expressible in an effector cell and remains largely unassociated with respect to the other polypeptide in the absence of ligand. The presence of specific ligand induces a stable interaction between the ligand

association domains of each polypeptide chain and facilitates interaction between the intracellular domains, which leads to a signaling event and activation of the effector cell expressing the polypeptide chains. As a result of these properties, improved chimeric receptors of the present invention display minimal constitutive activation in the absence of antigen and reduced responsiveness to soluble antigen. Such chimeric receptors are, therefore, particularly useful tools in the context of treating a variety of disorders, including various cancers, which are frequently characterized by elevated levels of circulating disease-associated antigens. Improved chimeric receptors of the present invention, therefore, remain "fully loaded" until they encounter an intended target cell expressing bound antigen.

Rejections under 35 USC § 112

Claim 39 has been rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In view of the amendments to the claims and applicants' arguments hereinbelow, the rejection, as it applied to claim 39, is respectfully traversed.

The Examiner has indicated that pHMF374 and/or pHMF367 are required to practice the invention as claimed. As is understood, the rejection appears to be based on the Examiner's assessment that these required elements are not sufficiently known and readily available to the public or obtainable by a repeatable method set forth in the specification. Applicants strenuously disagree with the Examiner in this regard. As indicated herein above, **both** pHMF374 and pHMF367 are disclosed in Figure 3, wherein components of these plasmids and the relative arrangement of the indicated plasmid components are clearly presented. Moreover, the specification describes in great detail the manner with which these plasmids may be generated. See the Example section at page 12, line 21 through to page 14, line 30, wherein a step wise method for constructing VH/CD8*/CD4 TM/CD4 and VL/CD8*/CD4 TM/TCR zeta chimeric receptors is found. The methodology presented includes the means by which the individual components (such as, for example, the CD4 TM) of these chimeric receptors are generated and/or

assembled; such means include PCR cloning and PCR assembly by standard techniques, which are described in the specification and are procedures of routine practice in molecular biology laboratories. The details presented include specific primers for PCR amplifying/cloning particular components and restriction enzymes that are used to generate compatible ends for subsequent subcloning steps.

As detailed in the specification, assembled chimeric receptor constructs are subcloned from pBluescript KS+® into the expression vector pEE6hCMV.ne on a Hind III to EcoR1 restriction fragment to generate plasmids pHMF367 and pHMF370. See page 14, line 35 through to page 15, line 2 and Figure 3. As described therein, the expression vector pHMF374 is constructed which expresses both separate chain chimeric receptor genes by subcloning a Bgl to Bam H1 fragment consisting of an hCMV promoter, Vl/CD8*/CD4 TM/TCR zeta and SV40 poly A site into the Bam H1 site of pHMF367.

It is noteworthy that pEE6 expression vectors, including the expression vector pEE6hCMV.ne, were known in the art well in advance of the priority date of the present application (May 6, 1998). This is evidenced by several references, which describe and utilize these expression vectors, including: Stephens and Crockett. 1989. Nucleic Acids Research 17:7110; McKnight and Classon 1992. Immunology. 75:286-92; Pease et al. 1993. Biochem Mol Biol Int. 29:339-47; Cosgrove et al. 1995. Protein Expr Purif. 6:789-98; and Hornick *et al.*1997. Blood 89:4437-47. Moreover, as indicated in the Hornick *et al.* reference (p. 4438, first column, first paragraph, lines 3-5), pEE6 expression vectors were commercially available in advance of the filing date of the present application. Copies of these references or abstracts thereof are submitted for the Examiner's consideration and are listed as Refs. **AE-AI** in the Supplementary Information Disclosure Statement (IDS) attached hereto. Thus, these references reinforce applicants' affirmation that the present specification viewed in the context of public knowledge available before May 6, 1998 fully satisfies the requirements set forth for enablement.

In view of the above, applicants assert that the specification and the scientific literature published in advance of the priority date of the application and submitted for consideration in the Supplemental IDS clearly support claims which are directed to pHMF374.

In view of the detailed description presented in the specification for making pHMF367 and pHMF374, the clarity of the diagrams depicting these expression vectors (see Figure 3), and common knowledge, applicants assert that an ordinarily skilled practitioner would certainly appreciate how to make the constructs following the repeatable method set forth in the specification and would be able to generate these constructs in stepwise fashion.

Claim 39 has been rejected under 35 USC § 112, second paragraph, for alleged indefiniteness. Specifically, claim 39 is allegedly indefinite for recitation of "Plasmid pHMF374 of Figure 3", a figure which the Examiner maintains is directed to "pHMF367". Applicants respectfully refer the Examiner to page 3 of Figure 3 having a header of FIG. 3 (contd.), wherein pHMF374 is depicted. In that pHMF374 is shown in Figure 3 and the schematic shown in this figure clearly indicates the characteristics of pHMF374, applicants assert that claim 39 as presented is definite. In view of the support presented in the specification for pHMF374 and characteristics thereof, the rejection of claim 39 under 35 USC § 112, second paragraph, for alleged indefiniteness is respectfully traversed.

In view of the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 34 and 39 under 35 U.S.C. §112 and withdraw the rejection.

Rejection Under 35 U.S.C. § 102

The Examiner has rejected claims 34 and 35 under 35 U.S.C. §102(b) as allegedly anticipated by Gross *et al.* (PNAS USA 86:10024-10028, 1989). This reference teaches the replacement of the variable regions of the T cell receptor (TCR) alpha and beta chains with antibody V_H and V_L domains in order to alter the specificity of TCR binding. The chimeric receptor that results contains the antibody variable domain, the TCR constant domain, the TCR transmembrane region and the TCR cytoplasmic domain. Retention of the TCR constant domains in the alpha and beta chains of the chimeric receptors described by Gross *et al.* results in the formation of disulphide bridges between the alpha and beta chains of such receptors when expressed in the membrane (see page 10027, column 2, penultimate line through to page 10028, column 1, first four lines). The alpha and beta subunits of the chimeric receptors of Gross *et al.* are, therefore, **constitutively**

associated prior to antigenic (ligand) exposure. Thus, Gross *et al.* do not disclose a chimeric receptor such as that of claim 34, wherein the spacer and/or transmembrane domains have been selected to remain unassociated in the absence of ligand.

Claims 34, 35, and 38 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by WO 96/23814. The WO 96/23814 patent application is, however, directed to a chimeric receptor containing a single chimeric polypeptide chain. It does not disclose a chimeric receptor containing two or more independent polypeptide chains that only associate in response to ligand binding. In embodiments wherein both V_H and V_L are required to form a binding site, the V_H is present on the chimeric receptor and the V_L is provided as the entire IgG light chain, not as a chimeric receptor. See, for example, page 18, lines 3-7. As described therein, dimers are constitutively generated via intermolecular disulphide bridges formed between the chimeric receptor and the IgG light chain. See, for example, page 18, lines 7-10. Moreover, the preferred strategy described in the WO 96/23814 application is directed to the use of a single chain chimeric receptor bearing a functional antigen binding site. See page 19, line 5. Thus, the WO 96/23814 patent application fails to describe a chimeric receptor as called for in claim 34, wherein the spacer and/or transmembrane domains have been selected to remain unassociated in the absence of ligand.

Claims 34 and 35 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by WO 92/10591 as evidenced by EMBASE accession number 2003166740 (Kinjo et al. J. Clinical Pathology, 2003, 56/2, 97-108). The WO 92/10591 patent application describes a single chain chimeric receptor and is, therefore, not relevant to claims 34 and 35 for the same reasons as described herein above with regard to the WO 96/23814 application. Again, there is no disclosure of a chimeric receptor containing two or more independent polypeptide chains that are only brought together by ligand binding. Indeed, the results disclosed in the WO 92/10591 application indicate that the receptors containing the extracellular and transmembrane domains of CD8, for example, exist as homodimers or homotrimers due to disulphide bonds formed between these domains which are present on distinct polypeptide chains. See, for example, page 24, lines 23-28.

The alleged applicability of EMBASE accession number 2003166740 (Kinjo et al. J. Clinical Pathology, 2003, 56/2, 97-108) to the present invention is not apparent to the applicants. Clarification regarding this reference is, therefore, respectfully requested. In that this reference fails to disclose a chimeric receptor containing two independent chimeric polypeptide chains, the association of which is triggered by ligand binding, it is,

apparent that the deficiencies of the WO 96/23814 patent application are not remedied by the disclosure of EMBASE accession number 2003166740 (Kinjo et al. J. Clinical Pathology, 2003, 56/2, 97-108).

Claims 34, 35, and 38 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by WO 96/24671. The WO 96/24671 patent application discloses a single chimeric receptor polypeptide chain. It does not disclose a chimeric receptor containing two or more independent polypeptide chains, the association of which is mediated by ligand binding. In embodiments wherein both V_H and V_L domains are required to form a binding site, the V_H is present on the chimeric receptor and the V_L is provided as a full-length IgG light chain, not as a chimeric receptor. See, for example, page 14, lines 22-25). In these circumstances, intermolecular Fc/hinge disulphide bonds are formed to produce dimers wherein the extracellular domain resembles that of an IgG. See page 14, lines 25-28.

In one example described in the WO 96/24671 patent application, the V_H region is used in the extracellular domain of a multispecific chimeric receptor (MSCR) and MSCR dimers are not formed. A binding site is only formed following introduction of a full-length Ig light chain. See page 14, line 28 through to page 15, line 3. Again, the preferred strategy is to introduce a single molecule bearing a functional antigen binding site (see page 15, lines 21-26), thus avoiding the "technical difficulties that may attend the introduction and coordinated expression of more than one gene construct into host cells". See page 15, lines 23-26.

As stated herein above, reference to EMBASE accession number 2003166740 (Kinjo et al. J. Clinical Pathology, 2003, 56/2, 97-108) and an explanation as to how this reference allegedly pertains to the present invention is not clearly presented in the Office Action. Clarification regarding this reference is, therefore, respectfully requested. Inasmuch as this reference fails to disclose a chimeric receptor containing two independent chimeric polypeptide chains that associate in response to ligand binding, it is clear that the disclosure of EMBASE accession number 2003166740 (Kinjo et al. J. Clinical Pathology, 2003, 56/2, 97-108) does not compensate for the deficiencies of the WO 96/23814 patent application.

Claims 34 and 35 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by WO 97/23613. The patent WO 97/23613 application describes recombinant chimeric receptors containing two or more different signaling components, a transmembrane

domain and a binding component. The receptors described in the WO 97/23613 application are specifically designed and selected to homodimerize. It is stated that "the spacer and transmembrane components are advantageously chosen to provide the chimeric receptor with 'multimerisation, particularly dimerisation capacity'." See page 7, lines 4-6.

The chimeric receptors of WO 97/26313, therefore, exist as dimers even in the absence of ligand and as a result, may signal constitutively. Thus, the WO 97/23613 patent application does not disclose a chimeric receptor such as that described in claim 34. Indeed, the WO 97/23613 patent application teaches away from the chimeric receptors of the present invention. According to the present invention, by careful selection of non-associating spacer and/or transmembrane domains each polypeptide chain in the chimeric receptor of the present invention can be expressed independently and remains unassociated in the absence of ligand. The receptor chains are only brought together by the stable interaction of the binding domains with the ligand, thus preventing constitutive signaling in the absence of ligand.

In view of the above, applicants contend that the rejection of claims 34, 35, and 39 under 35 U.S.C. §102(b) is unfounded and respectfully request that the rejection be withdrawn.

Rejection Under 35 U.S.C. § 103

The Examiner has rejected claims 34, 35, and 38 under 35 U.S.C. §103(a) as allegedly unpatentable over WO 97/23613 in view of Maniatis et al.

The Examiner has rejected claims 34, 35, and 38 under 35 U.S.C. §103(a) as allegedly unpatentable over WO 92/10591 in view of Maniatis et al.

The Examiner has rejected claims 34, 35, and 38 under 35 U.S.C. §103(a) as allegedly unpatentable over Gross et al. (PNAS USA 86:10024-10028, 1989), in view of Maniatis et al.

Arguments presented herein above with regard to rejection of claims 34, 35, and 38 under 35 U.S.C. §102(b) as allegedly anticipated by any one of WO 97/23613, WO 92/10591, or Gross et al. (PNAS USA 86:10024-10028, 1989) are equally well applied in the context of the above rejections under 35 U.S.C. §103(a). As described in detail herein, each of these references, when considered alone or in view of Maniatis et al., fails to teach or suggest a chimeric receptor containing two independent chimeric polypeptide

chains that are selected to associate only in response to ligand binding. Indeed, there is no teaching or suggestion in any of these references that there is any advantage to a chimeric receptor comprised of two chimeric polypeptide chains that do not associate prior to ligand binding.

Moreover, as described herein above, the disclosures of each of WO 97/23613, WO 92/10591, and Gross et al. (PNAS USA 86:10024-10028, 1989) includes significant guidance underscoring the advantages of designing chimeric receptors that dimerize constitutively. Inasmuch as claims 34, 35, and 38 of the present invention are directed to chimeric receptors comprising two chimeric polypeptide chains that do not associate prior to ligand binding, and none of the cited references describe such chimeric receptors or appreciate any advantages associated with the chimeric receptors of the present invention, it is apparent that these references do not impact any consideration pertaining to the non-obvious nature of the invention. Furthermore, the Maniatis et al. reference, which is cited in the context of using a plasmid vector, fails to remedy the fatal deficiencies of any one of WO 97/23613, WO 92/10591, or Gross et al.

In view of the above, applicants contend that the rejection of claims 34, 35, and 39 under 35 U.S.C. §103(a) is improper and respectfully request that the rejection be withdrawn.

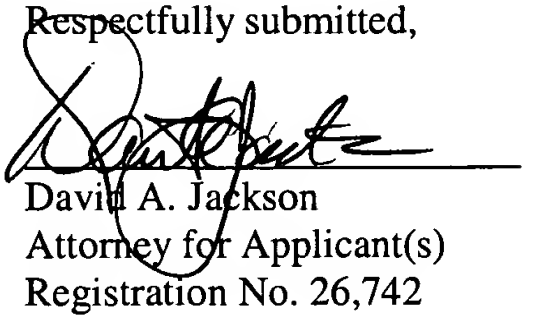
Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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Enclosures: Supplemental IDS and copies of five references cited therein
Petition for a One-Month Extension of Time